ANNOUNCEMENT OF DRAFT REQUEST FOR PROPOSALS (RFP)

TITLE: ACQUISITION OF MODIFIED VACCINIA ANKARA (MVA) VACCINE FOR THE STRATEGIC NATIONAL STOCKPILE

REFERENCE NUMBER: RFP-DHHS-ORDC-V&B-05-06

Purpose of Announcement

As provided for by FAR.5.205 entitled "Special Situations," a draft Request for Proposals (RFP) is being broadcast. The purpose of this announcement is inform potential interested individuals, institutions and organizations, of a draft project, and to solicit comments from interested parties with respect to the scope, design and requirements of this project.

This draft RFP is from the Department of Health and Human Services, Office of the Secretary, Office of Public Health Emergency Preparedness, Office of Research and Development Coordination. It is entitled Acquisition of Modified Vaccinia Ankara (MVA) Vaccine for the Strategic National Stockpile.

The urgent nature of this requirement requires an accelerated pace of development, testing, approval, and procurement of an emergency stockpile of vaccine. In the case of intentional smallpox release prior to licensure by the Food and Drug Administration (FDA)/Center for Biologics Evaluation and Review (CBER), it is anticipated that the investigational MVA vaccine could be administered under a "Contingency Use" Investigational New Drug (IND) protocol or Emergency Use Authorization (EUA), held by the Centers for Disease Control and Prevention (CDC). Vaccine acceptance into the SNS is solely dependent on the accumulation and submission of the appropriate data to support EUA and/or the use of the product under IND. However, all vaccine manufactured and acquired under this Contract must meet the regulatory deliverables as required for licensure.

Please note that proposals are not being solicited at this time. With this announcement, the Office of Research and Development Coordination (ORDC) is soliciting comments and recommendations on draft Statement of Work in order to: (1) determine interest in this solicitation; (2) assure that requirements included in the documentation will meet the intent of the solicitation; and very importantly, (3) identify or clarify what may appear to be problems, conflicts, or obstacles for an institution or organization that might otherwise wish to become a potential offeror. The responses from this announcement will be considered in the preparation of a RFP for this acquisition.

For prospective offerors information, it is anticipated that the final RFP will include proposal preparation instructions with the following page limitations: a limitation on the number of pages that address the base work requirements to 200 pages, and 200 pages for

accompanying appendices; and a limitation on the number of pages that address the optional work requirements to 50 pages, and 100 pages for accompanying appendices.

It is anticipated that one or two award(s) will be made under this requirement. The period of performance for the resultant contract award(s) will be five (5) years. The contract type will be a hybrid with firm fixed price items and some cost reimbursable items. There are options for maintaining cGMP capability (warm base), the purchase of additional quantities of vaccine, and obtaining data to support expanded clinical usage any one of which could result in a five (5) year extension to the period of performance.

We encourage you to respond electronically to Brenda Brooks, Contracting Officer, on this matter, using the Response Guidelines provided below, to indicate issues or elements you are particularly in favor of, or which you find problematic to the response capacity of your institution or organization. Electronic responses should be submitted by May 31, 2005.

Please note that the Government does not intend to award a contract based on this draft project annoucement or to otherwise pay for the information solicited. Although "proposal" and "offeror" are used in this Announcement, your response will be treated as information only. It shall not be used as a proposal.

TITLE: ACQUISITION OF MODIFIED VACCINIA ANKARA VACCINE FOR THE STRATEGIC NATIONAL STOCKPILE
REFERENCE NUMBER: RFP-DHHS-ORDC-V&B-05-06

Whether you review this draft RFP as a potential future offeror or as a fact-finding exercise, the ORDC is interested in your feedback. The ORDC is actively soliciting input to improve and refine this draft requirement and is seeking to gauge the degree of interest in this effort. **PROPOSALS ARE NOT BEING SOLICITED AT THIS TIME.** Candid questions and concerns elicited by this notice are encouraged. Please note that the Government will not provide individual responses to questions/inquiries. However, the extent to which a dialogue may be established with any individual or business entity concerning a given issue raised by this notice shall, for purposes of fairness and compliance with Agency regulations, be determined by the Contracting Officer after consultation with the cognizant ORDC Technical Program Office.

Examples of feedback may include, but are not limited to:

1. Level of interest in pursuing a prime contract with the U.S. Government, or a subcontract, consultant or other collaborative relationship with a potential prime Contractor, for this requirement. If there is no interest at this time, please explain why.

2. Comments, questions and/or concerns regarding the scope and/or design of the attached draft RFP.

Responses should be clear and succinct. We do not desire the submission of any technical or cost proposals. Any critique of the draft RFP should adequately describe concerns and offer recommendations and/or solutions, which might be used by the GOVERNMENT in refining the requirement. Critical technical concerns should be supported with questions posed in such a way as to point toward possible alternatives that may be pursued by the ORDC in refining some aspect(s) of the requirement.

Responses should be submitted electronically by Friday, May 31, 2005. All responses should include the name, position/title, telephone/extension, facsimile number(s), and electronic mail address(es) of the contact individual. The response should also identify the institution, organization, company, etc., and the complete street address (including, where applicable, location identifiers, e.g., office stop and room number) including zip code.

All response information should reference RFP-DHHS-ORDC-V&B-05-06 and be directed in writing via electronic mail to:

Brenda Brooks, Contracting Officer
E-mail: bbrooks@niaid.nih.gov
Phone: 301-435-2765
Facsimile: 301-402-0972

Additionally, please provide a copy to:

Matthew Brown, Contract Specialist
E-mail: mb629i@nih.gov
Phone: 301-451-3691
Facsimile: 301-402-0972

DRAFT REQUEST FOR PROPOSALS (RFP)

TITLE: ACQUISITION OF MODIFIED VACCINIA ANKARA VACCINE FOR THE STRATEGIC NATIONAL STOCKPILE

REFERENCE NUMBER: RFP-DHHS-ORDC-V&B-05-06

I) INTRODUCTION

Recent, significant changes in both the nature, regularity, and degree of the threat posed by the use of infectious agents as weapons of biological warfare have generated increased concern for the safety of the general American populace. With the deliberate exposure of citizens of the United States, postal workers, and other United States Government (USG) employees to *Bacillus anthracis (B. anthracis)* spores in 2001, there is an urgent need to stockpile appropriate and effective medical countermeasures to protect all U.S. citizens from the morbidity and mortality associated with infection from these instruments of terror. Despite the eradication of infectious smallpox disease and the cessation of mass vaccination programs, the threat of a terrorist related smallpox release remains a dire possibility.

The Federal Response Plan of the Department of Homeland Security designates the Department of Health and Human Services (HHS) as the lead agency for public health and medical response to manmade or natural disasters. In 2002, HHS established the Office of Public Health Emergency Preparedness (OPHEP). This office holds responsibility for implementation of a comprehensive HHS strategy to protect the civilian population from acts of bioterrorism and other public health emergencies.

Project BioShield, which provides new tools to improve medical countermeasures protecting Americans against a chemical, biological, radiological, or nuclear (CBRN) attack, was signed into law on July 21, 2004. It is anticipated that Project BioShield will ensure that resources are available to pay for "next-generation" medical countermeasures. Project BioShield will allow the government to buy improved vaccines or drugs. The fiscal year 2004 appropriation for the Department of Homeland Security included $5.6 billion over 10 years for the purchase of next generation countermeasures against anthrax and smallpox as well as other CBRN agents.

The Office of Research and Development Coordination (ORDC) in OPHEP has the primary responsibility within HHS to contract with industry for the advanced development and acquisition of licensable products for delivery into the Strategic National Stockpile (SNS). Examples of such products are recombinant Protective Antigen (rPA) Anthrax vaccine and next generation smallpox vaccines from attenuated vaccinia virus strains. These contracts will require the submission of a Biologics License Application (BLA), license supplements, long-term maintenance of the stockpiled products, and a long-term manufacturing base to continue replenishing the stockpile as product expires. Real-time stability data supporting a long-term expiration dating period

for the vaccine stored in the stockpile is considered important for the USG. This Request for Proposal (RFP) represents the first HHS request for acquisition of a Modified Vaccinia Ankara (MVA) vaccine. Future procurements are expected to take advantage of rapid advances in formulation, manufacturing and innovative delivery systems.

II) BACKGROUND

Variola virus, the etiological agent of smallpox, is considered to have been one the greatest scourges of human health. The mortality rate naturally-occurring of smallpox infection is approximately 30%, and individuals who recover from the infection frequently have disfiguring scars. It has been estimated that throughout recorded history more people died of smallpox than from all other infectious diseases combined. Fortunately, vaccination with a related, live, replicating, attenuated Orthopoxvirus (vaccinia virus) eventually led to the global eradication of this disease in 1979. Routine vaccination was halted shortly thereafter because the risks associated with vaccination outweighed the threat of the disease. Recent knowledge on the possible weaponization and availability of smallpox stocks to rogue nations has increased concern about the reemergence of this dreadful disease. As a result of this assessment, the U.S. Government has procured enough replication-competent smallpox vaccine to immunize for every U.S. citizen, if needed.

The currently licensed smallpox vaccine (Dryvax®) is presently employed to vaccinate U.S. military, lab workers, and first response personnel. Dryvax® has been in use for many years and has been shown to be highly effective in preventing smallpox infection among vaccinated persons. Because the vaccine contains live vaccinia virus (the origin of this vaccinia virus strain remains unknown, and it is different from both cowpox and variola), it replicates in the host and is associated with significantly higher rates of local and/or systemic reactions among healthy vaccinees than is seen with more commonly used childhood and adult vaccines. Common mild side effects seen with smallpox vaccine include redness and swelling at the site of vaccination, fever and myalgia. Although rare, more serious side effects include post-vaccinial encephalitis, eczema-vaccinatum, disseminated vaccinia and death. In addition, myopericarditis has been strongly associated with vaccine use, in adults. With the exception of post-vaccinial encephalitis and myopericarditis, the other listed major side effects are more commonly seen in immunocompromised persons and persons with certain skin conditions, particularly eczema. The number of U.S. citizens who are immunocompromised has increased over the years due to: 1) life-saving drugs and medical procedures which compromise the immune system such as those used in organ transplant or in the treatment of cancer and 2) the increased number of individuals infected with HIV. The documented increase in persons with a current or past history of eczema is unexplained. Dryvax® is presently contraindicated for non-emergency use in these potentially at-risk groups. The vaccine is also contraindicated for non-emergency use to all who have close household contact with individuals who are immunocompromised or have a history of eczema. In light of the increased risk of post-vaccination adverse events to these, and certain other groups (pregnant/lactating women, persons with autoimmune disease, and

their contacts), an effective but non-host-replicating smallpox vaccine has the potential to protect these groups from smallpox infection while decreasing serious adverse outcomes.

Modified Vaccinia Ankara is a live highly attenuated form of vaccinia virus developed in Germany during the smallpox eradication period (1964-1970) as a "pre-vaccine". It was administered by intradermal injection, followed by standard vaccination using scarification with Lister-Elstree strain of vaccinia virus one to two weeks later. The goal of the combined vaccination was to induce immunity with MVA that would subsequently reduce adverse reactions associated with the replicating vaccine. While this dual vaccination strategy was tested in over 150,000 individuals (many of whom were at risk for vaccination with the replicating vaccine) with no adverse events, it was never tested for efficacy in preventing smallpox in endemic areas.

The parent strain of vaccinia from which MVA was derived, termed CVA, was more virulent than other vaccinia strains. MVA was then derived by >500 serial passages in primary chick embryo fibroblasts (CEF). As a result of continuous passage *in vitro*, the viral genome suffered six major deletions and numerous mutations; of importance, MVA is missing at least two host-range genes required for growth in mammalian cells, and several genes essential for viral immune evasion. MVA is incapable of replicating in most mammalian cells, and data suggests that some strains of MVA can safely be administered to newborn mice, rabbits, chickens and immunosuppressed mice and primates. MVA has been shown in preliminary studies to protect nonhuman primates against challenge from monkeypox virus, and more recently has been used safely in investigational studies as a gene delivery vector for HIV and cancer vaccines.

In February 2003, two contracts were awarded by NIAID as a result of RFP-NIH-NIAID-DMID-03-44. The main objectives of this solicitation were to: (a) produce 5,000 doses of MVA vaccine under manufacturing conditions that would enable the government to file an Investigational New Drug (IND) application for this product, (b) assess the immunogenicity and protection against lethal Orthopoxvirus challenge provided by MVA in small animal models, (c) develop a clinical plan for MVA and initiate a Phase I clinical trial, and (d) develop a feasibility plan to manufacture, formulate, fill, test and deliver up to 30 million doses of MVA vaccine for the U.S. Government.

In September 2004, two additional contracts were awarded by NIAID as a result of RFP-NIH-NIAID-DMID-04-49. The primary purpose of this RFP was to continue the advanced development and manufacture of an MVA vaccine. It was intended to target MVA vaccine candidates that could be produced at a scale to support commercial manufacturing, and that had demonstrated safety and immunogenicity in extensive preclinical studies. Although licensure of an MVA vaccine is not planned within the timeframe of RFP-NIH-NIAID-DMID-04-49, all activities and studies conducted in response to this RFP shall be those required for a licensure path.

III) PURPOSE

The primary purpose of this Request for Proposal (RFP) is the acquisition of 20 million doses (in single-dose vials) of MVA vaccine for the Strategic National Stockpile (SNS). The primary use of this vaccine will be for pre-exposure prophylaxis of individuals considered to be at risk subsequent to a known or suspected smallpox virus release.

IV) SCOPE OF WORK

Independently, and not as an agent of the USG, the Contractor shall furnish all the necessary services, qualified personnel, materials, supplies, equipment, facilities, transportation and travel not otherwise provided by the USG as required to:

a) Manufacture and deliver to the SNS a minimum of 10 million and up to 20 million doses of "usable" MVA vaccine within the first 18 months of the Contract Award date (see Specific Technical Requirements below). The vaccine shall be provided in single-dose vials in frozen liquid suspension. The Sponsor, with concordance from the FDA/CBER, shall determine the optimal titer of virus per dose as determined in Phase 2 studies sponsored by the NIAID.
b) Perform accelerated and real-time stability assessments to support the proposed dating period of the Bulk Drug Substance (BDS) and a dating period of at least 5 years for the Final Drug Product (FDP), and conduct ongoing stability assessments to support extension of the product dating period;
c) Conduct supportive clinical trial(s) and animal studies to support an EUA, as specified by the FDA/CBER, for pre-exposure prophylaxis of healthy individuals considered to be at risk subsequent to a known or suspected smallpox virus release (i.e., primary indication);
d) Conduct supportive clinical trial(s) and animal studies to support an EUA, as specified by the FDA/CBER, for pre-exposure prophylaxis of immunocompromised individuals considered to be at risk subsequent to a known or suspected smallpox virus release;
e) Conduct Phase 3 clinical trial(s) and animal studies, as per FDA/CBER regulations, to support licensure of the product for pre-exposure prophylaxis of healthy individuals considered to be at risk subsequent to a known or suspected smallpox virus release (i.e., primary indication), including demonstration of safety and efficacy of an optimized dosing regimen, single or two-dose, based on supporting data to justify such a regimen;
f) Obtain FDA/CBER licensure for the clinical indication of pre-exposure prophylaxis of healthy individuals considered to be at risk subsequent to a known or suspected smallpox virus release, including post-licensure approval for use in pediatric and geriatric subjects;
g) Perform shipping validation studies, quality control and quality assurance monitoring on product in the SNS, and track/rotate inventory of the stored product through the end of the contract.

V) SPECIFIC TECHNICAL REQUIREMENTS: Advanced Development and Licensure of MVA Vaccine

The Contractor shall perform all the work required to manufacture and obtain FDA/CBER approval of a licensed MVA vaccine. **Payments to the Contractor will be solely dependent on the delivery to the SNS of "usable" MVA vaccine supported by a sufficient body of safety, efficacy, and cGMP manufacturing data to use under an EUA or Contingency Use IND protocol.**

Definition of Usable Product: For clarity, "usable" product must be the final formulation of drug product derived from a fully validated manufacturing process, i.e., consistency lot FDP. There must be a high degree of confidence, as determined by the FDA/CBER, that all manufactured units of FDP from successive lots will meet acceptable product specifications as demonstrated by comprehensive and satisfactory in-process and release testing. A minimum of three (3) consistency lots must be manufactured at commercial scale to demonstrate reproducibility and provide an accurate measure of variability among successive runs. The product must meet stability specifications to the satisfaction of FDA/CBER prior to entry into the SNS. Sufficient safety (non-clinical and clinical) and efficacy data (non-clinical and clinical serology), as per the recommendations of the Interagency Animal Study Group (IASG), posted on the NIH/NIAID website in April 2005, must be submitted to Contractor's IND prior to delivery of vaccine to the SNS to support use of investigational vaccine by the USG. The pivotal safety, immunogenicity, and efficacy data to support usable product and license requirements must be derived from studies using FDP produced from a fully validated manufacturing process. An ongoing stability program must be in place using a stability indicating assay(s) that has been agreed upon by FDA/CBER. The acceptance of the product for inclusion into the SNS for emergency purposes will be based upon review of ongoing data and mutual agreement with FDA/CBER, ORDC, and CDC, in consultation with the Contractor, that the above usability criteria have been met. These data will be the basis for FDA/CBER review and concurrence that the vaccine meets the definition of usable product. The Contractor shall conduct longer term studies on an on-going basis as needed for licensure and incorporate the requirements shown below into a work plan and timeline.

Requirement 1 – Vaccine Production and cGMP Compliance (**See Note # 8 to Offerors**)

a) The Contractor shall manufacture and deliver to the SNS MVA vaccine according to cGMP throughout the period of performance. The Contractor shall deliver a minimum of 10 million and up to 20 million doses of usable FDP within 18 months of contract award. The BDS and FDP shall be manufactured under cGMP conditions and meet the specifications determined by the FDA/CBER for licensure.

b) The Contractor shall provide all information requested to the Project Officer and/or the FDA/CBER in order to facilitate a cGMP inspection at the time of production of vaccine lots destined for the SNS.

c) The Contractor shall provide a proposal to FDA/CBER to utilize a single two-part label for both the investigative and licensed (final approvable label) phases of the product. This labeling strategy will not require re-labeling from an IND label to the FDA approved label once the BLA is granted. This proposal should also contain instructions for the end-user for both pre- and post-licensure scenarios, a mockup (including carton and shipper), and any/all labeling studies, and consistent with the proposal, and be provided to the FDA/CBER, as well as the Project Officer. The labeling strategy and mockup will address the use of product pre- and post-licensure.

d) The Contractor shall provide primary and secondary points of contact that will be available 24 hours per day, seven days per week, to be notified in case of a public health emergency.

Requirement 2 – Stability Testing of Finished Vaccine (**See Note # 9 to Offerors**)

a) The Contractor shall validate critical assays necessary for BDS and FDP release and stability testing, to assess immune response parameters for animals and humans, and for potency evaluation. Validation of all assays will be required for licensure; however, FDA/CBER will determine the validation of critical assay parameters for product use under a CDC-held IND protocol or EUA to be utilized in the case of a smallpox public health emergency. Validated analytical procedures shall be used irrespective of whether they are for in-process, release, immunogenicity and stability testing. Each quantitative analytical procedure shall be designed to minimize assay variation. Formal quality unit review of analytical test results shall be performed according to established quality standards and procedures.

b) The Contractor shall conduct accelerated and real-time stability studies, including potency testing, on the BDS lots stored by the Contractor and FDP lots placed in the SNS in conformance with FDA/CBER requirements throughout the contract lifetime. Storage temperature conditions of the FDP should be developed and tested with consideration given to the cost-effect storage and deployment requirements for the SNS.

c) Stability test results will support a product expiry dating period of at least 5 years. Testing will be performed in accordance with current regulatory guidelines.

d) The Contractor shall perform stability studies, including potency testing, to extend the product expiry dating period and request an extension of the dating period from FDA/CBER in a license supplement as appropriate.

e) At the discretion of the USG and independent of testing conducted by the Contractor, the USG reserves the right to conduct inspections and collect samples of product held by the Contractor and in the SNS.

Requirement 3 – Design of Safety, Efficacy, and Immunogenicity Studies, Including Execution of Studies to Support EUA. (**See Note # 10 to Offerors**)

a) The Contractor shall develop and submit non-clinical and clinical plans to support a CDC-held EUA for pre-exposure prophylaxis of (1) healthy individuals and (2) immunocompromised individuals considered to be at risk subsequent to a known or suspected smallpox virus release.

b) In addition, the Contractor shall develop, submit, and execute non-clinical and clinical plans to demonstrate safety and efficacy under the Animal Efficacy Rule ***(21 CFR 601.91)*** and human safety and immunogenicity studies adequate for U.S. licensure. These plans shall be designed in consultation with appropriate USG agencies and should support the licensure of MVA for pre-exposure prophylaxis of (1) healthy individuals and (2) immunocompromised individuals considered to be at risk subsequent to a known or suspected smallpox virus release. Further, these plans will include studies to demonstrate safety and efficacy of an optimized dosing regimen, single or two-dose, based on supporting data to justify such studies.

c) The Contractor shall submit a plan for conducting field studies under a CDC-held EUA, so as to evaluate the biological product's clinical benefit and to assess its safety when such studies are feasible and ethical. Such studies would not be feasible until an exigency arises.

Requirement 4 – Conduct of Safety and Efficacy Studies (**See Note # 11 to Offerors**)

The Contractor shall initiate and complete Phase 3 clinical trial(s) in support of a Biologics License Application for use of MVA. The initial BLA indication will be for pre-exposure prophylaxis of healthy individuals considered to be at risk subsequent to a known or suspected smallpox virus release.

a) All trials shall utilize usable vaccine and shall initiate only upon Project Officer approval and acceptance of plans and protocols by FDA/CBER.

b) The initial BLA should cover both genders within the age range of 18-55 years using the optimal dose regimen and schedule for prophylaxis.

c) Subsequent post-licensure studies are expected to extend the range of ages for which the vaccine is indicated, to include pediatric and geriatric subjects.

d) Vaccine efficacy shall be demonstrated with usable product in at least two animal models as per 21 CFR 601.91. (FDA Animal Rule) regulations.

e) The Contractor shall initiate Phase 4 post-marketing studies. As noted in the "Animal Rule," the Contractor shall submit a plan for conducting post-marketing studies at the time of license application. These post-marketing studies, when such studies are feasible and ethical, should include field studies, so as to verify and describe the biological product's clinical benefit and to assess its safety when used as indicated. Such post-licensure studies would not be feasible until an exigency arises. When such studies are feasible, the Contractor shall conduct such studies with due diligence.

Requirement 5 – Regulatory Submissions **(See Note # 12 to Offerors)**

a) To conduct Phase 3 clinical trials, the Contractor shall prepare and submit to the FDA/CBER, the required regulatory submissions (as they pertain to the IND and/or any Drug Master File(s) as specified in, but not limited to, 21 CFR 312, 314.420, and 601) for lot consistency, safety, and immunogenicity in normal, healthy volunteers. Such volunteers may be integrated with any ongoing clinical trial(s) for the clinical indication of pre-exposure prophylaxis of healthy individuals considered to be at risk, subsequent to a known or suspected smallpox virus release. Further, it is anticipated that the Contractor will provide the necessary data to CDC to support the submission of a CDC-held IND and/or EUA.

b) The Contractor shall prepare and submit an original BLA for MVA vaccine in order to obtain FDA/CBER licensure for pre-exposure prophylaxis of healthy individuals considered to be at risk subsequent to a known or suspected smallpox virus release (i.e., primary indication). The Contractor shall review the criteria for Fast Track designation, consult with FDA/CBER, and then seek such designation during the IND stage for this indication, if appropriate. At the pre-BLA meeting, the Contractor shall request priority status for review of the MVA vaccine BLA for this indication, if appropriate, to allow a "rolling BLA" (i.e. review of the BLA will start before all parts of the BLA have been submitted).

c) The Contractor shall prepare and submit a supplement to the BLA for MVA vaccine in order to extend the range of ages for pre-exposure prophylaxis of healthy individuals considered to be at risk subsequent to a known or suspected smallpox virus release, to include pediatric and geriatric subjects.

d) All regulatory submissions must comply with current FDA/CBER regulations and policies.

Requirement 6 –Shipment to SNS and Storage **(See Note #13 to Offerors)**

a) The Contractor will assume responsibility for the cost of shipping finished product to the SNS. The USG will assume responsibility for the cost of finished product long-term storage and emergency distribution of the finished product. The USG shall incur only the storage costs while the product is held within the

USG's control. The product shall remain in storage at the Contractor's facility until the USG requests a scheduled pick-up of finished product.

b) The Contractor shall ensure that the delivery follows cGMP procedures to maintain the integrity of the product en route. The Contractor shall perform/execute all necessary pilot transfers and shipping validation studies prior to first shipment of product. The Contractor shall file the necessary documentation to the FDA/CBER for the safe movement of the product to include any protocol deviations en route.

c) The Contractor shall be responsible for the secure and segregated storage of held intermediates and the FDP prior to lot release and subsequent shipment to the USG. However, while the product is in long-term storage with the USG (i.e., in SNS), the Contractor shall continue to be responsible for all quality control/quality assurance monitoring and subsequent reporting necessary to insure appropriate storage conditions of the product until said product is licensed. The Contractor, via this contract with the USG, will be expected to establish a written Quality Agreement as to the manner in which the product will be stored within the specific USG stockpile facility (ies) that have been identified post contract award. In addition, this Quality Agreement will outline the responsibilities of both the Contractor and the USG (i.e., SNS- Quality Control). These documents shall be drafted and signed by both parties prior to the transport and storage of the product.

Requirement 7 – Disposition of Vaccine Inventory

Upon expiration or termination (including partial termination) of this contract, the USG may effect final distribution of any vaccine remaining in storage at the Contractor's facility by any one or combination of the following methods:

a) The USG may elect to direct the Contractor to ship to a consignee(s) designated by the USG, all vaccine remaining in storage at the Contractor's facility.

b) The USG may offer the vaccine to be repurchased by the Contractor at the original purchase price.

c) The USG may elect to request the Contractor to destroy the vaccine in storage at the Contractor's facility. If the Contractor is required to destroy the vaccine, an equitable adjustment may be required.

The USG may elect to handle disposition of expired vaccines by any one or combination of the following methods:

a) The USG may elect to request the Contractor to ship all expired vaccines and vaccines scheduled to expire within 30 calendar days to the USG to the location specified by the USG.

b) The USG may elect to request the Contractor to destroy the BDS or FDP in storage at the Contractor's facility. If the Contractor is required to destroy the product in storage at the Contractor's facility, an equitable adjustment may be required.

Nothing in this requirement 7 shall be interpreted to affect the Governments rights pursuant to the following clauses:

FAR 52-249-2 and 52.249-8.

Requirement 8 – Maintaining a MVA Vaccine Production Capacity

The Contractor shall manufacture, release, maintain and monitor one (1) lot per year of BDS, and corresponding fill/finish of the FDP, at commercial scale for the life of the contract in order to maintain cGMP capability.

Requirement 9 – Security of Contract Operations

The work performed for development, manufacturing, storage and distribution will be performed under a detailed security plan that ensures against theft, tampering or destruction of the specific pertinent documents. The Contractor shall develop a written Draft Security Plan, for the protection of physical facilities, using, for example, fencing, controlled access, surveillance equipment, 2-person integrity rule, tamper evident packaging, and armed guards. The Contractor shall submit the Draft Security Plan to the Contracting Officer and Project Officer within 30 calendar days after award of the contract. The Draft Security Plan shall describe the procedures to be utilized to control the general internal operations of the firm and a description of Offeror's facility (ies) in which the work will be performed-including any subcontractors. Also, the Contractor shall submit to the Government a list of all employees involved in production under this contract. This list shall include the employee's full name, date of birth, and Social Security number (or other identifying number as appropriate, e.g., Passport number). The Government shall retain this list in confidence, and use it only to compare the information contained therein against the Government's list or lists of known or suspected terrorists or threats. The Draft Security Plan shall also include the Contractor's plans for conducting background investigations for all employees and subcontractors who will have access to the development, manufacturing, and storage of the product.

This plan shall ensure confidentiality and integrity of and timely access by authorized individuals to data, information and information technology systems, and consistent with OMB Circular A-130, Appendix III. This plan shall include the security measures to be used to protect the vaccine to be stored at the Contractor's facility (e.g., refrigeration/freezer alarm systems, backup electrical power generator systems, etc.), and the contingency plan to accommodate any manufacturing and storage problems caused by natural or man-made disasters, power loss, refrigerant loss, equipment failures, etc.

The Project Officer and the Information Protection and Systems Security (IPASS) Coordinator will review the plan and submit comments to the Contractor within ten (10) calendar days after receipt. The Contractor shall revise the Security Plan, if required, and

submit a Final Security Plan to the Government within ten (10) working days after receipt of the Government's comments. Performance of work under this contract shall be in accordance with this written Security Plan.

Requirement 10 – Information Technology Security

The Contractor's IT Security Plan shall be included as part of the Technical Proposal and will be incorporated into any resultant contract. Performance of work under this contract shall be in accordance with this written IT Security Plan.

The Contractor will be responsible for data sharing, in both paper and electronic formats, with other Government Agencies and support services contractors, per USG direction.

Other Requirements – Meetings and Conferences (See Note #14 to Offerors)

The Contractor shall participate in regular meetings to coordinate and oversee the contracting effort as requested by the Project Officer. Such meetings may include, but are not limited to, meetings of all Contractors and Subcontractors to discuss clinical study designs, site visits to the Contractor's facilities, and meetings with individual Contractors and other HHS officials to discuss the technical, regulatory, and ethical aspects of the program. The Contractor shall provide data, reports, and presentations to groups of outside experts and USG personnel as required by the Project Officer in order to facilitate review of contract activities.

V. STATEMENT OF WORK - OPTIONS

OPTIONS: The Government may exercise any of the below items. Exercise of an option will also extend the contract period of performance by up to five (5) years.

1. Produce, release, maintain and monitor one (1) lot per year of BDS, and corresponding fill/finish of the FDP, at commercial scale to maintain vaccine cGMP capability (warm base) for the life of the contract extension (Requirement 8).
2. Manufacture and deliver to the SNS up to an additional 60 million doses of the MVA vaccine provided in single-dose vials as a frozen liquid suspension. Consideration by the USG for this option will be based on safety, efficacy, and cost information to support use of MVA vaccine in individuals contraindicated for vaccination with live, replication-competent smallpox vaccines.
    a. The BDS and FDP shall be manufactured under cGMP conditions and meet the specifications determined by the FDA/CBER for licensure (Requirement 1a).

    b. The Contractor shall provide all information requested to the Project Officer and/or the FDA/CBER in order to facilitate a cGMP inspection at the time of production of vaccine lots destined for the SNS (Requirement 1b).

    c. The Contractor shall provide a proposal to FDA/CBER which consists of a labeling strategy and plan for re-labeling product from IND material to FDA/CBER licensed material. This proposal should also contain a mockup (including carton and shipper), consistent with the proposal, and be provided to the Project Officer, as well as the FDA/CBER. The labeling strategy and mockup will address the use of product pre- and post-licensure (Requirement 1c).

3. Conduct Phase 3 clinical trial(s) in support of a Biologics License Application Supplement for expanded use of MVA. The expanded clinical indication will be for pre-exposure prophylaxis of <u>immunocompromised</u> individuals considered to be at risk subsequent to a known or suspected smallpox virus release.

    a. All studies shall utilize vaccine manufactured by the final scale process and shall initiate only upon Project Officer approval and acceptance of plans and protocols by FDA/CBER (Requirement 4a);

    b. Obtain approval for a BLA Supplement for the expanded indication using the optimal dose regimen and schedule for prophylaxis;

c. The Contractor shall initiate Phase 4 post-marketing studies in the immunocompromised population. As noted in the "Animal Rule," the Contractor shall conduct post-marketing studies, such as field studies, to verify and describe the biological product's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. Such post-marketing studies would not be feasible until an exigency arises. When such studies are feasible, the Contractor shall conduct such studies with due diligence (Requirement 4e).

4. The Contractor shall conduct real-time stability studies, including potency testing, on the BDS lots stored by the Contractor and FDP lots placed in the SNS in conformance with FDA/CBER requirements beyond the base period of the contract (Requirement 2b).

5. The Contractor shall initiate Phase 4 post-marketing studies in healthy individuals (i.e., primary indication). As noted in the "Animal Rule," the Contractor shall submit a plan for conducting post-license studies at the time of license application. These post-marketing studies, when such studies are feasible and ethical, should include field studies, so as to verify and describe the biological product's clinical benefit and to assess its safety when used as indicated. Such post-licensure studies would not be feasible until an exigency arises. When such studies are feasible, the Contractor shall conduct such studies with due diligence (Requirement 4e, **See Note # 11 to Offerors**).

Deliverables and Reporting Requirements

A. Deliverables

The following are considered **Base Contract deliverables** under this contract.

1. A minimum of 10 million and up to 20 million single-dose vials of usable MVA vaccine (see Section 2. Specific Technical Requirements**)** in frozen liquid suspension to be delivered to the SNS to support use under a CDC-held IND and/or EUA for both healthy and immunocompromised individuals to be delivered within 18 months of contract award date.
2. An FDA/CBER approval letter for the BLA for MVA vaccine for pre-exposure prophylaxis of healthy adult individuals considered to be at risk subsequent to a known or suspected smallpox virus release (i.e., primary indication).
3. An FDA/CBER supplement approval letter for use in pediatric and geriatric subjects.
4. Evidence, including a summary of salient results, of an ongoing Quality Control/Quality Assurance Program for the monitoring of SNS stored product and ongoing stability testing of the retained lots of product in SNS over the life of the contract or the expiration date of the vaccine, or until vaccine is used, whichever comes first.
5. Draft and Final Security Plans in advance of initiating work at any facility performing under this contract.
6. Written Quality Agreement between the Contractor and the SNS Quality Control Unit within 6 months of award.

All Technical Reports as described below.

The following are considered **Contract Option deliverables** under this contract.

1. One (1) lot per year of BDS, and corresponding fill/finish of the FDP, at commercial scale for the life of the contract in order to maintain cGMP capability.
2. Up to 60 million single-dose vials of usable MVA vaccine (see Section 2. Specific technical requirements) in frozen liquid suspension to be delivered to the SNS to support use under a CDC-held IND and/or EUA and subsequent licensure.
3. An FDA/CBER approval letter for a BLA license supplement for an expanded clinical indication including use in immunocompromised individuals.

4. Evidence, including a summary of salient results, of an ongoing Quality Control/Quality Assurance Program for the monitoring of SNS stored product and ongoing stability testing of the retained lots of product in SNS for the duration of the contract option.

5. Clinical reports of post-marketing studies for both healthy and immunocompromised individuals. These post-marketing studies, when such studies are feasible and ethical, should include field studies, so as to verify and describe the biological product's clinical benefit and to assess its safety when used as indicated. Such post-marketing studies would not be feasible until an exigency arises.

B. Reporting Requirements

The Contractor(s) shall submit to the Contracting Officer and to the Project Officer technical progress reports covering the work accomplished during each reporting period. These reports are subject to the technical inspection and requests for clarification by the Project Officer. These shall be brief and factual and prepared in accordance with the following format:

(1) Monthly Technical Progress Reports: On the fifteenth of each month for the previous calendar month, the Contractor shall submit a Monthly Technical Progress Report to the Project Officer and the Contracting Officer. A monthly report will not be required for the period when the final report is due. The Contractor shall submit one copy of the Monthly Progress Report electronically via e-mail. Any attachments to the e-mail report shall be submitted in Microsoft Word, Excel, Project or compatible versions. Such reports shall include the following specific information:

The contract number and title, the period of performance being reported, the Contractor's name and address, the author(s), and the date of submission;

Section I – An introduction covering the purpose and scope of the contract effort during the period of performance being reported;

Section II – The report shall detail, document, and summarize the results of work done during the period covered, including problems encountered and corrective actions taken. This shall include the information listed below that is applicable for the performance period during the month being reported.

a) Scale up to full production capacity assessment, including raw material procurement status;
b) Quality control/quality assurance monitoring;
c) FDA/CBER inspections and consultation results or recommendations;
d) Storage and stability studies for expiration date results (accelerated, stress, and long-term storage conditions);
e) Security assessment, problems and recommendations;

f) Progress, results, and final reports of expanded human safety studies;
g) Progress, results, and final reports of efficacy studies performed in animals if following the Animal Rule, or clinical studies required for Accelerated Approval;
h) Progress, results, and final reports of any other studies deemed necessary by FDA/CBER;
i) Progress in providing data to CDC to support CDC submission of a CDC-held IND protocol and/or EUA to be utilized in the case of a smallpox event;
j) Progress in obtaining FDA/CBER approval/licensure for pre-exposure prophylaxis of healthy individuals considered to be at risk subsequent to a known or suspected smallpox virus release (i.e., primary indication);
k) Progress in execution of any product disposition directions provided by the USG;
l) Progress, results, and final reports of any necessary additional animal and human studies to obtain expanded labeling in special populations, including pediatric and geriatric populations;
m) Potency and stability testing results;
n) Inventory report of total number of vaccine syringes in storage during the month, to include: lot number, expiration date, and bulk quantity (if applicable);
o) Quantity of out-of-date FDP, assessment and recommendations to replacement FDP orders to maintain required stockpile quantities;
p) Physical storage facilities (Contractor and SNS) assessments;
q) Overall project assessment, problems encountered and recommended solutions, etc.

Section III – An explanation of any difference between planned progress and actual progress, why the differences have occurred, and, if behind planned progress, what corrective steps are planned. The project plan and schedule, with accompanying Gantt chart, will be updated in each Monthly Report and compared to the locked project baseline.

(2) Final Report – By the expiration date of the contract, the Contractor shall submit a comprehensive Final Report that shall detail, document, and summarize the results of the entire contract work. The report shall explain comprehensively the results achieved.

NOTES TO OFFERORS

1. It is contemplated that the contract awarded will be fixed price, with some cost reimbursable elements. The table below describes the anticipated fixed price and cost reimbursable elements, and the basis and schedule of payment for those elements. The fixed price basis for the Final Drug Product will be based upon real-time stability data supporting a long-term expiration dating of the Final Drug Product. The conditions of a fixed price basis for the Final Drug Product will be negotiated based on existing product characterization data presented by the Offeror and future conditions to meet as agreed to by the Offeror and the USG. If an unusual circumstance can be documented by the Offeror to justify other than fixed price reimbursement for a fixed price element, this documentation should be submitted with the business proposal for consideration during negotiations.

Element of Cost	**Payment and Order Type**	**Basis for Payment**	**Payment Schedule**[1]
Requirement 1 Vaccine Production and cGMP Compliance	Firm Fixed Price	Included in base price per delivered dose of usable final drug product	Upon USG acceptance of doses for the SNS
Requirement 2a, 2b Stability Testing of Finished Vaccine	Firm Fixed Price	Included in base price per delivered dose	Upon USG acceptance of doses for the SNS
Requirement 2c Stability Testing of Finished Vaccine	Firm Fixed Price	Supplement to price per dose	Upon FDA/CBER approval of dating period
Requirement 2d Stability Testing of Finished Vaccine	Cost Reimbursement	Progress payments based on cost incurred	Upon completion of milestone(s)
Requirement 3 Design of Safety and Efficacy Studies	Firm Fixed Price	Included in base price per delivered dose	Upon USG acceptance of doses for the SNS
Requirement 4a,4b,4d Conduct of Safety and Efficacy Studies	Firm Fixed Price	Included in base price per delivered dose	Upon USG acceptance of doses for the SNS
Requirement 4c, Conduct of Safety and Efficacy Studies	Cost Re-imbursement	Progress payments based on cost incurred	Upon completion of milestone

[1] Offeror may propose an incremental payment schedule related to USG acceptance of doses for the SNS

Requirement 5a Regulatory Submissions	Firm Fixed Price	Included in base price per delivered dose	Upon USG acceptance of doses for the SNS
Requirement 5b, 5c Regulatory Submissions	Firm Fixed Price	First and second supplement(s) to price per dose for FDA/CBER approval	Upon FDA/CBER approval of BLA and supplement and re-labeling
Requirement 6 Shipment to SNS and Storage	Firm Fixed Price	Included in base price per delivered dose	Upon USG acceptance of doses for the SNS
Requirement 7 Disposition of Vaccine Inventory	Firm Fixed Price	Included in base price per delivered dose	Upon USG acceptance of doses for the SNS
Requirement 9 Security of Contract Operations	Firm Fixed Price	Included in base price per delivered dose	Upon USG acceptance of doses for the SNS
Requirement 10 Information Technology Security	Firm Fixed Price	Included in base price per delivered dose	Upon USG acceptance of doses for the SNS
Monthly and Final Reports	Firm Fixed Price	Included in base price per delivered dose	As required in the Deliverables and Reporting Requirements

[1] Offeror may propose an incremental payment schedule related to USG acceptance of doses for the SNS

Optional Items

The table below describes the anticipated optional contract elements, the type of reimbursement, and the basis and schedule of payment for those elements. Optional Contract item 2 is Firm Fixed price. These items represent product intended for additional populations, and may be exercised by the USG subject to the availability of funds and dependant on the demonstration of further safety and immunogenicity profiles.

Element of Cost	**Payment and Order Type**	**Basis for Payment**	**Payment Schedule**
Option 1 Maintaining a MVA Vaccine Production Capability	Cost Reimbursement	Progress payments based on cost incurred	Upon completion of milestone

Option 2 Additional Doses	Firm Fixed Price	Included in base price per delivered dose of usable final drug product per amount ordered.	Upon USG acceptance of doses for the SNS
Option 3 Additional Clinical Studies	Cost Reimbursement	Progress payments based on cost incurred	Upon completion of milestone
Option 4 Extended Stability	Cost Reimbursement	Progress payments based on cost incurred	Upon completion of task
Option 5 Conduct of Phase 4 Post-licensure Studies	Cost Re-imbursement	Progress payments based on cost incurred	Upon completion of task
Monthly and Final Reports	Firm Fixed Price	Included in base price per delivered dose	As required in the Deliverables and Reporting Requirements

2. Any resultant contract shall include the clauses applicable to the selected Offeror's organization and type of contract awarded as required by Public Law, Executive Order, or acquisition regulations in effect at the time of execution of the proposed contract.
3. Activities to be performed in response to this RFP and consistent with the period of performance must be clearly delineated. Pricing for delivered doses should consider only activities proposed in response to this RFP that are consistent with the associated objectives, requirements, time lines and period of performance delineated in this RFP. Note that data provided in support of the delivered IND doses will be based on a vaccine and manufacturing process for the final product and process. Either preclinical or clinical studies or both may be necessary to bridge between cGMP product lots manufactured by the same process but at progressively larger scale. The Offeror should consider this in developing an approach, schedule, and pricing in response to this RFP.
4. Each proposal (i.e., one each for RFP requirements and options) shall include a Contractor's Work Plan(s) (CWP) that describes the manufacturing, testing, clinical and regulatory activities to be performed in response to the RFP requirements and options. A single Gantt chart shall be provided to include all activities described in the CWP; these activities should be linked to fulfillment of Requirements 1-10. A separate Gantt chart shall be provided to include all activities described in the Options CWP; these activities should be linked to fulfillment of Options 1-5. The delivery schedule for doses of final drug product should be indicated in the CWP. The CWP(s) must contain sufficient detail to permit reviewers to make a realistic evaluation of the Offeror's likelihood of success. Technical detail should be such that the production output and the animal and clinical testing information requested for these activities require only minor changes after contract award.

5. The USG recognizes that some Offerors may have already completed some of the activities identified in the Statement of Work. In such instances, the technical proposal must include sufficient information to support this claim and to allow for appropriate technical evaluation.
6. Proposals shall include two separate compliance matrices, one each to show where all RFP Requirements and Options have been addressed in the technical and business proposals.
7. Due to the urgent need to protect the American public against agents of bioterrorism, and the considerable investment by the USG in research and development required to acquire the MVA vaccine inventory that is the subject of this RFP, the USG expects and requires that the Offeror take steps necessary to secure access to intellectual property, know-how, and tangible materials prior to contract award that the Offeror needs to fulfill its obligation under the contract. The Offeror shall submit as part of its Business Proposal documentation on the Offeror's access to intellectual property necessary to fulfill obligations under the contract. Accordingly, in determining the Offeror's capability to perform the contract, the USG will consider evidence that the Offeror has secured access to such intellectual property, know-how and tangible materials.
8. The manufacturing plan in the CWP(s) shall include:
    a. Details of the process to scale-up production, including data to support the approach, i.e., documentation of successful scale-up of similar product class or data from intermediate scales of production.
    b. Timeline for production and delivery of 10 - 20 million doses of product, within the first 18 months of the contract award date, and timelines for production and delivery of additional 20, 40, and 60 million doses (Option 2).
    c. Cost of production per single-dose vials for 10, 20, 40, 60, 80 million doses.
    d. Labeling strategy proposal for submission to FDA/CBER to utilize one label for the investigative and licensed (final approvable label) phase of the product. This submission must also contain instructions for the end-user, drafts of the product label and all carton/shipper labeling.
9. The plans for stability testing of the Bulk Drug Substance and Final Drug Product in the CWP shall include details for accelerated and real-time stability testing and replenishment of the vaccine as needed in consultation with the managers of the USG stockpile. It is the Contractor's responsibility to develop and execute a formal written agreement with SNS personnel and repository site personnel to outline all responsibilities to maintain product quality and integrity during the investigative phase of stored product. Offerors shall validate all assays necessary for product release and stability prior to licensure; however FDA/CBER will determine the validation requisite of critical assay parameters for use under the Contingency Use IND protocol. The Offeror shall submit all available real-time and accelerated stability data for the bulk drug substance and final drug product with their proposal and the stability data will be evaluated with regard to indicators of long-term stability.
10. The CWP shall contain safety and efficacy plans based on the most current and available information as a result from ongoing discussions with FDA/CBER. Plans

shall include assumptions on the number of volunteers required for the clinical studies and the number of animals and study design for the non-clinical studies. The plan must provide information about the contract research organization (CRO) proposed to conduct the clinical trials, including information about clinical personnel, laboratory procedures, proposed sites, and time lines for their completion. The plan shall describe the operational procedures the company will follow to ensure adequate oversight of the clinical trial, timely and accurate report of the information to the FDA/CBER, structure and responsibilities of a data and safety monitoring board, as well as policies of how data will be processed, shared, and published. The plan shall specify how the HHS would be kept apprised of progress and communication with the FDA/CBER, including processes to ensure the USG may co-monitor or provide independent audit of the clinical trials.

11. The Offeror must include as part of their proposal a plan or approach to post-licensure study commitments in the event such studies become ethical and feasible.

12. The CWP shall include a regulatory plan for all required submissions to the FDA/CBER. The regulatory plan should include all regulatory milestones to support submission of the IND and BLA.

13. The USG shall incur all facility storage costs while the product is stored in a USG identified storage facility. However, the manufacturer maintains ultimate responsibility for the product during storage and transport. The USG will choose the facility or facilities - it will be the responsibility of the Contractor to establish a written agreement with SNS Quality Control to remain engaged with, and responsible for, the product while stored with the USG.

14. Offerors shall assume a 2-day visit every 2 months for five people to the HHS office in Washington, DC. The HHS reserves the right to conduct site visits when deemed necessary. OFFERORS DETERMINED TO BE IN THE COMPETITIVE RANGE upon completion of the technical review will be subject to audits of cGMP compliance of manufacturing facilities, and audits of the status of validation of assays for in-process, release, immunogenicity and stability testing. These pre-award site visits are tentatively scheduled to occur in mid-September 2005.

15. The HHS may also schedule visits to the Contractor's facilities during contract period of performance. In addition, the HHS may convene an independent group composed of *ad hoc* experts and USG personnel that will provide HHS insight regarding manufacturing, testing, and regulatory issues; the Contractor will be required to supply information to these experts upon request.

16. If Offerors cannot obtain sufficient insurance coverage, and intend to seek indemnification from the USG, the indemnification request may be submitted as part of the response to this proposal. Indemnification requests shall be prepared in accordance with FAR 50.403-1. The Offeror(s) request to DHHS for indemnification will not be considered as part of the evaluation process.